CURRENT AND EVOLVING APPROACHES FOR PERMEABILITY ENHANCEMENT OF BCS CLASS III DRUG THROUGH LIPID BASED DELIVERY SYSTEM

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DECLARATION

I hereby declare that this synopsis report submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which to a substantial extent has been accepted for the award of any other degree or diploma of the university or other institute of higher learning, except where due acknowledgment has been made in the text.

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INTRODUCTION

The scientific substructure of medicinal compounds known as BCS used to categories medications according to their solubility and permeability through the biological membrane. The intestinal permeability, solubility, and dissolution of the drug component are three important characteristics that affect how quickly and how much the drug is absorbed from oral solid dosage forms. Together, they make up the BCS mechanism.[1].

The principle of BCS elaborated the drug compound yield profile which produces the same concentration profile among the gastrointestinal (GI) tract and after the administration of drugs orally it produces same plasma profile in the result. This theory can be lined up in the following equation [2].

$$\mathbf{J = P_w \times C_w}$$

J*:* Flux through the mucosa of the stomach,

P_w: Intestinal permeability

C_w: Ratio of concentration at the gut wall.

As per the scientific framework of Biopharmaceutical Classification System (BCS) divides medicinal molecules into the following categories based on their solubility and permeability.

Class I: high permeability & high solubility

In the class first, drug molecules have excellent solubility and permeability, and medications are effectively absorbed. In this class, the rate of absorption typically exceeds the rate of excretion.

Class II: high permeability & low solubility

In the class second, drug molecules have strong permeability but poor solubility, and their thermodynamic rate limits their bioavailability.. In this class of BCS, A correlation is found between the bioavailability of *in vivo* parameters and salvation of the *in vitro* parameters.

Class III: low permeability & high solubility

In the class third, drug molecules only partially pass through the gut barrier due to that absorption of the drugs in the systemic circulation is limited but the drug is more soluble and solvated in the nature.

Class IV - low permeability & low solubility

In the class fourth, drug substances have limited solubility and permeability which produces a poor bioavailability of the class III drugs. These drugs are not absorbed in the intestinal mucosa due to their low permeation and aqueous solubility rate.

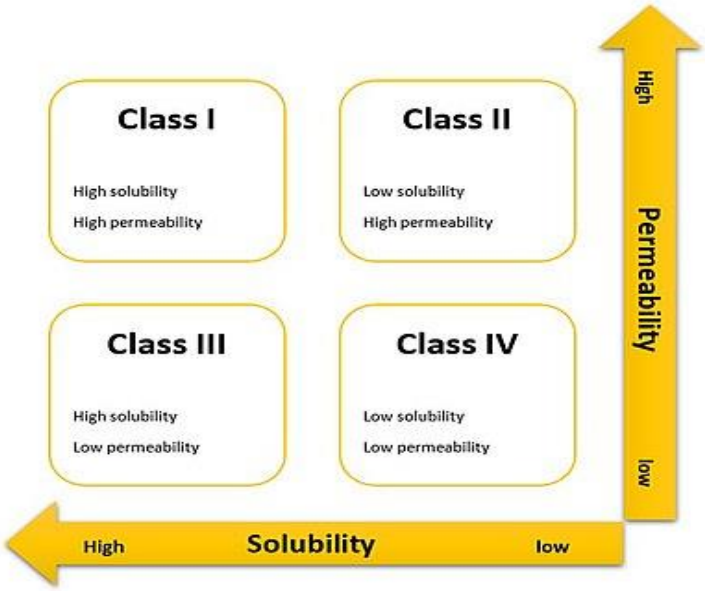

Figure 1. Classes of BCS

Solubility: The bioavailability of medication compounds is greatly influenced by the solubility of pharmacological components. Pharmaceutical compounds are contemplated more soluble when their dose strength is solublizing more in the 250 ml of the aqueous media or less amount in the pH range (1 – 7.5).

These estimated volume of aqueous media about 250 ml derived from the study of model bioequivalence protocols which provide calculated information for the prescription of the drug product to the human volunteers.

Gothoskar AV et. al. elaborated that solubility of any drug compound can be interpret, when amount of drug travel in the aqueous media and equilibrium is achieved in the middle of aqueous media and surplus compound (undissolved drug substance) at the given temperature and pressure.[3] A drug compounds are considered more maximum dose strength soluble when used in aqueous media with a volume of 250 ml or less and a pH range (1 – 7.5).

Table 1. Solubility standards

Descriptive Term (Solubility Definition)	Parts of Solvent Required for One Part of Solute	Solubility Range (mg/mL)	Solubility Assigned (mg/mL)
Very soluble (vs)	<1	>1000	1000
Freely soluble (fs)	from 1 to 10	100–1000	100
Soluble (s)	from 10 to 30	33–100	33
Sparingly soluble (sps)	from 30 to 100	10–33	10
Slightly soluble (ss)	from 100 to 1000	1–10	1
Very slightly soluble (vss)	from 1000 to 10000	0.1–1	0.1
Practically insoluble (pi)	>10000	<0.1	0.01

Permeability: The measurement of mass transfer rates across human intestinal membranes and the degree of medicinal drug absorption in humans are used to define permeability class limitations both directly and indirectly. These include the use of non-human technologies that can forecast drug absorption in the people. The drug substance is considered to be extremely permeable when the quantity of absorption in humans is anticipated to be 90% or more of the administered dose based on a mass-balance analysis or in comparison to an intravenous dose.

A drug molecule enters the intestinal epithelium and travels to the systemic circulation through a process known as permeability. Three main pathways exist for molecules to cross the epithelium: active transport, which is carrier-mediated; passive diffusion, which is concentration-dependent; and thirdly, specialised pathways like endocytosis and paracellular transport. Most medication absorption happens passively, by diffusion.

The degree of absorption identified in human pharmacokinetic experiments, such as absolute bioavailability or mass balance, is a more appropriate basis upon which to build the estimate of permeability.

Table 2. IVIVC expectations based on BCS class

Class	Permeability/ Solubility	Absorption rate control step	IVIVC
Class I	High /High	Gastric emptying	IVIVC expected if dissolution rate is slower than gastric emptying rate. Otherwise limited or no correlation.
Class II	High /Low	Dissolution	IVIVC expected if invitro dissolution rate is similar to invivo dissolution rate, unless dose is very high.
Class III	Low /High	Permeability	Absorption is rate determining and Limited or no IVIVC with dissolution.
Class IV	Low /Low	Case by case	Limited or no IVIVC expected

DRUG DELIVERY VIA ORAL

Oral drug delivery is the most common technique of drug administration due to its simplicity, patient preference, cost effectiveness, and convenience of mass production of oral dosage forms. Around 60% of marketed, established small molecule medicines are administered via the oral route. Current estimates place the global market share of all pharmaceutical formulations intended for human consumption at close to 90% for oral formulations. Around 84% of the top-selling pharmaceuticals are orally delivered, with a $35 billion market valuation and a 10% yearly growth rate. [8]

Orally administered medications can also be targeted to particular areas within the gastrointestinal (GI) tract for the localised treatment of pathological conditions like stomach and colorectal cancers, infections, inflammations, bowel diseases, gastro-duodenal ulcers, and gastroesophageal reflux disorders..

ADVANCED PERMEABILITY TECHNIQUES:

Bile Salts:

Bile, which contains chenodeoxycholic acid, glycine, and taurine conjugates of cholic acid, emulsifies fat, accelerates lipolysis, and makes it easier to transfer lipid products across the intestinal mucosa's immobile water layer by micellar solubilization. Taurine conjugates are more hydrophilic than glycine conjugates, which are more hydrophilic than free bile salts, in decreasing order of hydrophilicity. The quantity of hydroxyl groups affects how polar a substance is. Although bile salts can bind to calcium, the strength of their binding reduces with increasing hydrophilicity.

Complex of cyclodextrin inclusion:

The cyclic oligosaccharides known as cyclodextrins (CDs) are made up of d (+) glucopyranose units joined together by [1,4] glucosidic linkages. Owing to their distinctive structures — hydrophilic outer surfaces and hydrophobic cavities lined with protons—they naturally possess the ability to form inclusion complexes with a wide range of molecules. Drugs and drug candidates with high apparent water solubility and rapid dissolution can interact with CDs to augment these properties. Drugs with poor oral bioavailability are made more bioavailable using CD complexation. The improvement in oral bioavailability and the solubility also influence the rate of dissolution.

Derivatives of chitosan:

A biocompatible, non-toxic polymer called chitosan is used in a number of drug delivery processes, including the absorption of hydrophilic macromolecular drugs. The permeability of peptide drugs via mucosal epithelia, paracellular can be increased by protonating chitosan (pH 6.5). The penetration and absorption of neutral and cationic peptides across intestinal epithelia are enhanced by TMC (trimethyl chitosan chloride). Similar to protonated chitosan, TMC increases intestinal permeability through the same method. It interacts with chemicals of tight junctions in a reversible manner, creating paracellular pathways.

SMEDDS or (self-micro-emulsifying drug delivery systems):

Drug delivery devices that self-microemulsify can improve the GI absorption of BCS class IV medications, which are poorly permeable. These systems typically consist of isotropic blends of oils, surfactants, and cosolvents/co-surfactants. As substances are introduced into the GI system, they are diluted with digestive fluid, and the agitation caused by gastric motility causes a fine oil-in-water (o/w) micro emulsion to form (SMEDDS).

Prodrugs:

Prodrugs are the byproducts of drug molecules that undergo an in-vivo enzymatic or other biochemical transition to release the pharmacological activity of their parent drug. Prodrugs have historically been used to enhance the physicochemical and pharmacokinetic features of pharmacologically active drugs. Prodrugs offer options to get over formulation and drug transport obstacles include Inadequate oral absorption, rapid pre-systemic metabolism, low aqueous solubility, physical and chemical instability, and insufficient tissue permeability. [20]

Improving passive diffusion:

It is known that, in addition to other characteristics like partition coefficient, or log p values, of the majority of drugs has a significant impact on the permeability across cell membranes, similar to molecular size and concentration gradient. [21]

Enhancing active transportation:

Prodrugs that target certain membrane transporters are created with structural characteristics that would enable one of the natural transporters found at the intestinal epithelium to take them up. Targeting specific endogenous transporters is essential for highly polar, charged drugs that could not exhibit passive diffusion as a primary absorption mechanism.

Techniques based on nanotechnology

For improving the distribution of pharmaceutical medication formulations, nanotechnology-based techniques have recently attracted the most intense investigation. Nanotechnology-based

products are expected to significantly increase the bioavailability of many medications because of the perception that transmembrane permeability is increased by tiny particle size (_100 nm).

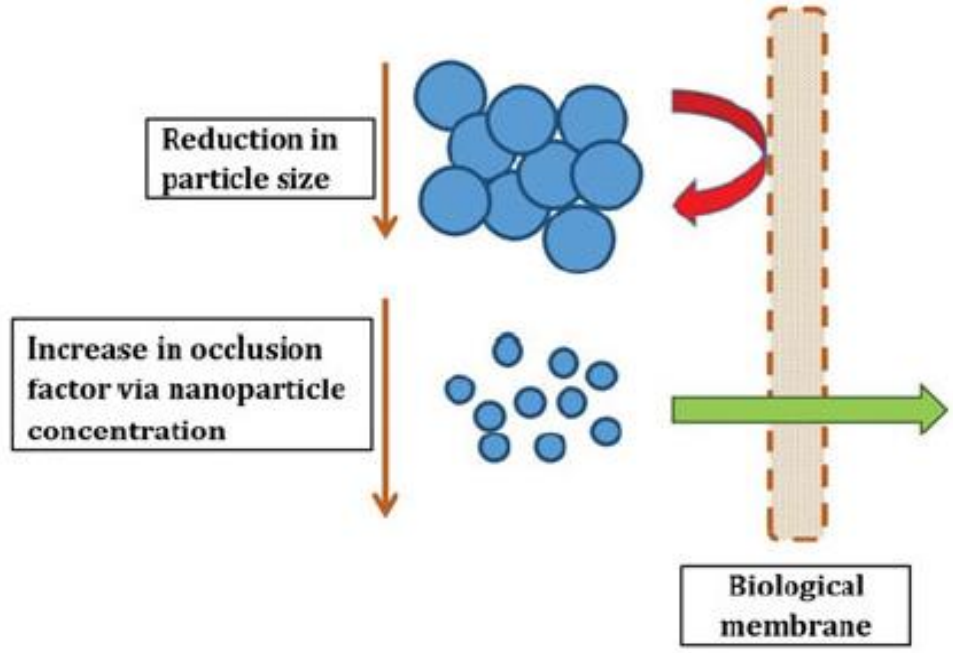

Figure 2. Occlusion factor and particle size

Nanoparticles

Recent medical and scientific research has concentrated on using nanoparticles to make medications more permeable. This method, which was initially developed with the goal of delivering anti-cancer medicines, has grown in popularity as a result of reports that it can also be used to carry nucleic acids, peptides, etc. in order to treat a range of disorders[23]. This method was developed in response to the disadvantages of therapeutic interventions involving macro- or micromolecules.

Nanoemulsion

Nanoemulsions are the best option for in the field of nanotechnology. Due to their ability to be created from excipients with solubilizing or even permeability boosting qualities, nanoemulsions are effective delivery systems for medicines that are weakly permeable and/or extremely

lipophilic. They reduced inter- and intra-individual unevenness for a range of medicines and increased gastrointestinal absorption, similar to conventional emulsions. Furthermore, because of their enormous interfacial area, they exhibit exceptional drug release capabilities.

Drug-polymer conjugates and versatile carrier systems, and smart drug delivery

Designing a multipurpose medication delivery system, and more specifically, capable of switching "on" or "off" specific activities as needed is necessary to achieve appropriate drug penetration and buildup in the target organ or tissue [24]. Few achievements have been documented despite numerous attempts to create such a drug delivery system based on nanotechnology, such as liposomes or nanoparticles.

Drug delivery methods that self-emulsify at the nanoscale: (SNEDDS)

The phrase "self-emulsification" refers to a self-explanatory anhydrous homogenous liquid mixture made up of oil, a surfactant, a medicine, and a coemulsifier or solubilizer that, when diluted with water and gently stirred, spontaneously forms. SNEDDS, which are nanoscaled, provide a potent substitute for the more traditional oral formulations of lipophilic drugs. It is anticipated that this system will swiftly self-emulsify in the stomach's watery contents.

This results in the medicine being introduced as a solution within nanosized oil droplets. Faster medication release throughout the GI tract would result from the stomach's quick emptying of these tiny droplets. Another benefit of SNEDDS over straightforward oily solutions is that they provide a significantly wider a zone that acts as an interface between oil and water to divide the drug and make it easier to disperse.

SNEDDS is independent of the function of bile salts, enzymes, and/or additional effects connected to the stomach's (fed/fasted) condition. As a result, SNEDDS can provide more consistent plasma concentration levels by reducing the variability in absorption rate and extent.

TARGETED DISEASE

1) **Hypertension:** Hypertension also known as high blood pressure (HBP), is primarily brought on by an ongoing rise in blood pressure in the heart's arteries, which increases the force that blood flows give to the artery walls. Despite the fact that high blood pressure is a chronic illness with few outward signs, it can nevertheless lead to serious health issues and, in certain cases, fatal cardiac conditions like angina pectoris, stroke, and heart attacks. Given that it is mostly brought on by inactivity, stress, and unhealthy eating patterns, among other lifestyle disorders, hypertension is a condition that is linked to lifestyle disorders.

Around 30 to 40 percent of persons worldwide have hypertension condition, according to research. Where obesity, hypertension, and other linked issues are the main causes for concern. Some of the most popular drugs include alpha-blockers, calcium-channel blockers, central agonists, peripheral adrenergic inhibitors, vasodilators, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers used to treat hypertension. Diuretics like thiazides, beta-blockers, indapamide, chlorthalidone, etc.

In order for lipid-based drug delivery systems to be effective against hypertension disease and increase the permeability of BCS class III of antihypertensive medicines, permeation enhancers should have the desired features of being pharmacologically inert by the materials (which shows poor permeability)

2) **Diseases caused by microbes and their resistance:** Microorganisms, which are very minute and invisible to the naked eye, are generally referred to as bacteria, fungus, protozoa, and viruses. Several germs are more dangerous and capable of causing serious illnesses known as pathogens that have a long-term negative impact on human health. Yet, some bacteria are benign and do not result in microbial infections. Many illnesses are brought on by microbial cells, and the majority of these microorganisms might have substantial negative consequences on the body of each patient. Microorganisms can easily infect host cells and cause disease through their pathogenicity. Even the most

recent research indicates that these tiny microbes may indirectly cause some chronic diseases and non-infectious diseases.

Antimicrobial resistance (AMR): Many bacteria cells are resistant to the majority of antimicrobial medications, posing a significant and growing burden on the healthcare system. Several projections anticipate that AMR will be a leading cause of mortality globally. It seems that a lot of pathogenic microorganisms are able to produce and build up resistance to a lot of antimicrobial drugs. The following are some significant drug resistance mechanisms: altered drug targets, constrained drug uptake, and deactivation of the drug candidate. Certain bacteria can be born with these kinds of mechanisms, while others can learn them.

The focus of additional research should stay on nanoemulsion assisted medication delivery, which is more promising and a novel alternative instrument to investigate and combat antimicrobial diseases and their resistance.

3) **Diabetes mellitus**: High blood sugar is a chronic, lifelong metabolic illness that is of great concern to the world's health. According to a recent assessment, diabetes has risen to alarming proportions and is largely to blame for the high death rate worldwide. The Federation of International Diabetes' most recent studies estimate that 470 million persons globally suffer from excessive blood sugar. According to projections, there will be approximately 578 million people globally living with high blood sugar by 2030, and this number will rise to 700-750 million by 2050. In this case, greater and more effective action is required to combat this pandemic disease.

Type 2 diabetes mellitus, which is primarily distinguished by high blood glucose levels known as hyperglycemia, is the major condition of pathogenesis in high blood sugar. Type 2 diabetes mellitus occurs when insulin secretion from the islet cells is insufficient against a background of insulin resistance.

LITERATURE REVIEW

Table 3. Review of literature

AUTHOR NAME	TOPIC	CONCLUSION
Chavda HV et. al, (2010)	Biopharmaceutics Classification System	The BCS profile primarily serves as a tool to direct the development of numerous oral drug delivery methods.
MohdYasir et. Al, (2010)	Biopharmaceutical Classification System :An Account	BCS offers a more effective method for evaluating and approving the quality of pharmaceutical items. Class II and III, BCS applications are more difficult, but they provide better chances down the road.
Vivek S. Dave et. Al, (2016)	Current approaches for the improving oral permeability of BCS Class III drugs	A viable option to raise the permeability of pharmaceuticals that have a low permeability is offered by approaches to nanotechnology..
Alan Parr. et. A.l, (2015)	The Effect of Excipients on the Permeability of BCS Class III Compounds and Implications for Biowaivers.	The results of five regularly used excipients' effects should be utilised to establish bio waivers for the BCS Class third drugs.
Yasuhiro Tsume et. Al., - 2010	The Biowaiver Extension for BCS Class III Drugs: The Effect of Dissolution Rate on the Bioequivalence of BCS Class III Immediate-Release Drugs Predicted by Computer Simulation.	Current dissolving standards are more stringent and now BCS class III pharmacological substances in IR dosage forms.
Ching-Ling Cheng et.. Al., - 2004	Biowaiver extension potential to BCS Class III high solubility-low permeability drugs: bridging evidence for metformin immediate-release tablet.	In-vivo bioequivalence testing can be waived by using the profile of in-vitro dissolution as a guide.

Deepa Nakmode et.. Al., - 2022	Fundamental Aspects of Lipid-Based Excipients in Lipid-Based Product Development.	Lipid-based administration has a huge potential to increase the bioavailability and oral absorption of low permeability medicines.
GanparajuVaishnavi et. al, (2021)	Review On Permeation Enhancers in Drug Delivery Systems.	Across the membrane, a complex made of lipoproteins improved permeability and oral bioavailability.
Neelam Poonia et. al, (2016)	Nanostructured lipid carriers: versatile oral delivery vehicle	Increasing the bioavailability and oral permeability.

AIM AND OBJECTIVES

Aim

The purpose of the current study is to create a "Current and Evolving Approaches for Permeability Enhancement of BCS Class III Drug through Lipid Based Delivery System"

By considering the facts, the project study aim-

- Increase the intestinal permeability with low toxicity profile.
- Increase the bioavailability
- Increase the stability
- Drug release in controlled and targeted way
- Reduce Dose frequency

Objectives

A. To develop a lipid-based medication delivery strategy to increase the permeability of BCS class III medicines.

B. To explore analytical methods of development, validation and contemplation.

C. To explore and develop new method of preparation of drug delivery system modulated through the carriers.

D. To formulate the drug-enclosed medication delivery system with self-nanoemulsification (SNEDDS).

E. Optimization and decision of best formulation using various optimization techniques.

PLAN OF WORK

1. Literature review.
2. Selection and procurement of drug, oil/permeation enhancers, surfactants, co-surfactants and other excipients.
3. Pre-formulation studies
    - ✓ Characterization of drug and carriers/excipients
    - ✓ Spectroscopic studies
    - ✓ Fourier transforms infrared (FT-IR) spectroscopy
    - ✓ Nanoemulsification behavior of carriers/excipients
    - ✓ Phase solubility studies
        - ➢ Drug-Lipid Partitioning Modeling
    - ✓ Physical analysis (thermal behavior) of drug
        - ➢ DSC
        - ➢ XRD
4. Formulation of SNEDDS loaded with BCS class III drug
    - ✓ Pseudo ternary phase diagram studies
5. Characterization of optimized formulation of SNEDDS loaded with BCS class III drug
    - ✓ Fabrication of lipid based complex loaded with drug/formulation
    - ✓ Aqueous dilution and pH on SNEDDS
    - ✓ Chemical analysis by HPLC
    - ✓ Dissolution/Release testing and dispersion mechanism
    - ✓ Droplet size by zetasizer
    - ✓ Polydispersity index (PDI)
    - ✓ Zeta potential determination
    - ✓ Percentage Transmittance Studies
    - ✓ Time for self-nanoemulsification

- ✓ Surface morphology and structure by TEM
- ✓ Determination of entrapment efficiency
- ✓ Rheological & conductometric analysis
- ✓ Drug content determination

6. Kinetic models
7. Stability studies
    - ➢ Degradation behaviour, Shelf-life and date of expiry
8. Permeation studies
    - ✓ *In-vitro* studies
        - ➢ Caco-2 cell line permeability studies
        - ➢ Lipolysis studies (Analysis of Post-digested Products)
    - ✓ Ex-vivo studies
        - ➢ Phospholipid membrane of inverted sac of rat
9. Pharmacokinetic studies
    - ✓ *In-vivo* studies
        - ➢ Pharmacokinetic/Pharmacodynamic studies in 6-8 week old male rats

EXPECTED OUTCOMES

There is a large and pressing need for study in oral absorption of BCS class third medicines/chemicals, which have low permeability and limited bioavailability. Medicines in this BCS class have reduced intestinal membrane permeability, which is assumed to be the phase that limits medication absorption rates. Ion-pairing, permeation enhancers, prodrugs, and nanotechnology-based technology are some of the new methods being employed to increase permeability.

The use of targeted carriers mediated transport has shown some promise and may be more effective in increasing intestinal membrane permeability. Research frequently demonstrates that the medication delivery method based on nanotechnology offers a promising and efficient instrument to improve the permeability of pharmaceuticals with low permeability. The reduction in particle size caused by nanosize and nanoencapsulation methods leads to an increase in drug permeability. To use this nanotechnology-based scientific work and achieve improved results, numerous clinical trials are still ongoing.

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